Gulf War and Health – Institute of Medicine Reports

Testimony of

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and
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Good morning Mr. Chairman and members of the subcommittee. Thanks to Congressman Shays, Congressman Kucinich and members of the house Subcommittee on National Security, Emerging Threats and International Relations for your concern about veteran's health. My name is Lynn Goldman. I am a professor of environmental health sciences and epidemiology at the Bloomberg School of Public Health at Johns Hopkins University in Baltimore and chair of our program in applied public health. Prior to joining Hopkins in 1999 I served for six years at the US Environmental Protection Agency (EPA) as Assistant Administrator for the Office of Prevention, Pesticides and Toxic Substances. My primary training is in pediatrics and epidemiology. I also have served as Chair of two Institute of Medicine (IOM) Gulf War committees: the committee that is currently working on the report *Gulf War and Health: Review of the Medical Literature Relative to Gulf War Veterans Health*, and the committee that produced the report *Gulf War and Health: Fuels, Combustion Products, and Propellants*. Additionally, I was a member of the committee that produced *Gulf War and Health: Insecticides and Solvents*. Because of my experience, the IOM requested that I testify about the approach taken by those committees, as well as other Gulf War and Health committees and Vietnam Veterans and Agent Orange (VAO) committees.

Those reports are part of a series of studies conducted by the IOM, a division of The National Academies, which have investigated the health effects of exposures that might have occurred during the Gulf War. They continue a long

history of the IOM applying its and its volunteers' scientific expertise to assist the Department of Veterans Affairs by evaluating scientific evidence and drawing conclusions regarding health effects associated with exposures to which our nation's veterans might have been exposed. On the basis of my own experience, it is my personal opinion that members of the committee take their responsibility to assess the scientific data in a fair and unbiased manner very seriously.

Today I would like to focus on two main points. First, from the perspective of a committee member and chair, how the IOM committee process works and the independence of IOM committees and second, the approach taken by the Gulf War committees, in particular the use of animal data.

IOM committees are comprised of expert volunteers and function independent of government oversight. At no time during the conduct of the Gulf War studies on which I was involved has anyone outside of the National Academies, including the Department of Veterans Affairs and the Department of Defense, and veterans, influenced the committee deliberations or the outcomes of the studies. Indeed the only outside guidance we have received has been in the form of (1) the legislation enacted by congress and signed into law by the President mandating that these studies be conducted, and (2) the scope of work that was established for each individual committee. Those items are indicated in the charge to the committee which is included in each report.

For each of the Gulf War reports, the expert committee members evaluated and interpreted literally thousands of peer-reviewed scientific publications that were identified through searches of databases. On the basis of their analyses and deliberations, the committees reached consensus conclusions on the potential associations between health outcomes and the agents of concern.

To fulfill the goals of the legislation, the approach taken to conduct the Gulf War studies is modeled after the approach taken for the Veterans and Agent Orange series of reports. At the same time, each newly-formed committee has needed to grapple with tailoring an approach to the challenges posed by the specific scientific issues put forward in the scope of work. Also, one difference between the Agent Orange studies and the Gulf War studies is the addition of a category of association, one of causality, to clarify that there is a difference scientifically between an association of an agent with a health outcome and an agent causing a health outcome. This category enhanced the scientific clarity of the committees' reports but did not change the criteria set forth by Congress. In practice, that category has rarely been invoked.

Each committee has needed to determine how to evaluate the various kinds of scientific evidence that are available. That decision is scientifically-based and is made by the committee with no external restrictions. When

available and of acceptable quality, epidemiology studies that have evaluated health effects in human populations exposed to chemicals of concern have been of great relevance to the work of all of these committees. However, for some outcomes and exposures, for example, contact dermatitis from exposure to certain chemicals, clinical case reports have played an important role; in most other circumstances such case reports have not been deemed acceptable.

Tables summarizing the committees' conclusions are presented in the Executive Summary of each Gulf War report. I submitted those tables as an appendix to the written portion of this testimony (see Appendix A).

We are aware that you are concerned about whether and how animal data have been utilized in our evaluations. Because of my previous involvement in a regulatory agency, I am well aware of the primary importance of such data in toxicological risk assessments for many chemicals, pesticides and radioactive materials. However, the various IOM committees, which have included toxicologists, have consistently agreed that, in general, animal data should not be used as a sole basis for drawing conclusions regarding health outcomes in humans. Why should this be the case? There are three reasons.

First, although animal data may indicate which category of health outcomes might occur in humans, it does not answer questions about specific medical diagnoses. Take vinyl chloride, a known human carcinogen. In humans it causes a rare cancer called angiosarcoma of the liver. But in laboratory rats it

causes an array of other cancers as well, including cancer of the zymbal gland, an organ that humans do not even possess. While such animal studies would be expected to give a more accurate determination of the potency of such a chemicals (given the lack of precise exposure measurements in human studies of vinyl chloride workers) it is only the human study that would provide the level of detail that is needed to conclude about specific health outcomes in humans. This issue is especially relevant to health outcomes like cancer and birth defects.

Second, animal studies may be carried out in ways that are not relevant to the Gulf War experience. Whereas the exposures in the Gulf were short term exposures to relatively low levels of chemicals and pesticides, most animal studies involve chronic doses to high levels of chemicals over much of a lifetime of an animal. These models are not appropriate to the experience in the Gulf.

Third, the Gulf War committees have often relied on pre-existing toxicology reviews for their reports. The Gulf War committees have been faced with evaluating the potential health effects of dozens of compounds that might have been used in the Gulf War. In some cases, prior expert committees have conducted extensive, peer-reviewed evaluation processes; these include reviews sponsored by: the Agency for Toxic Substances and Disease Registries (ATSDR), the EPA, the National Toxicology Program (NTP) and the World Health Organization (WHO). In such cases, where the effects of those chemicals in animals are well established and not contentious, Gulf War

committees have relied heavily on those summaries rather than consulting the thousands of original toxicology articles. If a toxicology study was particularly critical, such as an animal carcinogenicity study and the committee wanted more detail regarding the study than provided in a review document, the committee would evaluate the original study. In their reports, committees refer readers to summaries and reviews of the toxicology literature and provide details of any particularly relevant studies.

In closing I want to reiterate the main points of this testimony. First, the IOM committees that prepared the Gulf War reports work independently and decide as a committee how to approach the charge that they are given. Committees have a great deal of latitude in the interpretation and approach to its charge. Second, each committee decides how it will use epidemiology and toxicology data. In general, where adequate epidemiology data have been available, committees have decided that those data are the most appropriate on which to draw conclusions regarding the relationship of exposures to specific chemicals and potential health outcomes in humans. This process has been a productive one in that it has provided the Veteran's Administration with a wealth of information about the potential associations between agents in the Gulf War and the likelihood of subsequent adverse health effects in veterans. At the same time, as I noted in the preface to the last report that I chaired, which is attached (Appendix B), this is a process that is deserving of careful reassessment to

assure that the scientific expertise of the country is effectively engaged in the mission of assuring the health and wellbeing of our veterans.

I would like to thank you for inviting me to testify before this Subcommittee on National Security, Emerging Threats, and International Relations. Your careful scrutiny of this process is most welcome, I would be happy to answer any questions you have.

APPENDIX A:

Summary of Conclusions from Gulf War and Health Reports

TABLE 1 **Gulf War and Health Conclusions from Vols. 1, 2, 3 and Sarin Update**

TYPE OF CONCLUSION	GW&H Volume #	AGENT	HEALTH EFFECT
Sufficient Evidence of a Causal Relationship	2	Benzene	Acute leukemia Aplastic anemia
	1, Sarin	Sarin	Dose-dependent acute cholinergic syndrome that is evident seconds to hours subsequent to sarin exposure and resolves in days to months
Sufficient Evidence of an Association	1	Anthrax vaccination	Transient acute local and systemic effects
	2	Benzene	Adult leukemia
	1	Botulinum toxoid vaccination	Transient acute local and systemic effects
	3	Combustion products	Lung cancer
	2	Propylene glycol	Allergic contact dermatitis
	1	Pyridostigmine bromide	Transient acute cholinergic effects in doses normally used in treatment and for diagnostic purposes
	2	Solvents	Acute leukemia
Limited/Suggestive Evidence of an Association	2	Benzene	Non-Hodgkin's lymphoma
	2	Carbamates	Non-Hodgkin's lymphoma
Limited/Suggestive Evidence of an Association (continued)	3	Combustion products	Bladder cancer Cancers of the nasal cavity and nasopharynx Cancers of the oral cavity and oropharynx Incident asthma Laryngeal cancer Low birthweight/intrauterine growth retardation and exposure during pregnancy Preterm birth and exposure during pregnancy
	3	Hydrazines	lung cancer
	2	Insecticides	Allergic contact dermatitis
	2	Organophosphorus insecticides	Adult leukemia Non-Hodgkin's lymphoma OP poisoning and long-term neurobehavioral effects (that is, abnormal results on neurobehavioral test batteries and symptom findings)
	1	Sarin at doses sufficient to cause acute cholinergic signs	Symptoms and subsequent long-term health effects
	Sarin	Sarin at doses sufficient to cause acute cholinergic signs	Symptoms and a variety of subsequent long-term neurological effects

TYPE OF CONCLUSION	GW&H Volume #	AGENT	HEALTH EFFECT
	2	Solvents	Adult leukemia Bladder cancer Chronic glomerulonephritis Hepatic steatosis Multiple myeloma Myelodysplastic syndromes Neurobehavioral effects (that is, abnormal results on neurobehavioral test batteries and symptom findings)
	2	Tetrachloroethylene and dry-cleaning solvents	Bladder cancer Kidney cancer
Inadequate/ Insufficient Evidence to Determine Whether an Association Exists	2	Benzene	Myelodysplastic syndromes
	3	Combustion products	Colon cancer Esophageal cancer Female breast cancer Female genital cancers (cervical, endometrial, uterine, and ovarian cancers) Hepatic cancer Hodgkin's disease Kidney cancer Leukemia Male breast cancer Melanoma Multiple myeloma Myelodysplastic syndrome Nervous system cancers Non-Hodgkin's lymphoma Ocular melanoma Pancreatic cancer Prostatic cancer Rectal cancer Stomach cancer Testicular cancer

TYPE OF CONCLUSION	GW&H Volume #	AGENT	HEALTH EFFECT
Inadequate/ Insufficient Evidence to Determine Whether an Association Exists (continued)	3	Fuels	Bladder cancer Cancers of the nasal cavity and nasopharynx Cancers of the oral cavity and oropharynx Colon cancer Esophageal cancer Female breast cancer Female genital cancers (cervical, endometrial, uterine, and ovarian cancers) Hepatic cancer Hodgkin's disease Kidney cancer Laryngeal cancer Lung cancer Male breast cancer Melanoma Multiple myeloma Myelodysplastic syndromes Nervous system cancers Non-Hodgkin's lymphoma Nonmelanoma skin cancer Pancreatic cancer Prostatic cancer Rectal cancer Stomach cancer Testicular cancer
Inadequate/ Insufficient Evidence to Determine Whether an Association Exists (continued)	2	Insecticides	Aplastic anemia Brain and other central nervous system cancers Kidney cancers Lung cancer Pancreatic cancer Prostate, testicular, or bladder cancers Soft tissue sarcomas
	2	Insecticides and solvents	Amyotrophic lateral sclerosis Alzheimer's disease Hepatobiliary cancers Hodgkin's disease Irreversible cardiovascular outcomes Male or female infertility after cessation of exposure Multiple myeloma Parkinson's disease Peripheral neuropathy Persistent respiratory symptoms or impairment after cessation of exposure
	2	Insecticides (parental preconception exposure)	Childhood leukemias, brain and other central nervous system cancers, and non-Hodgkin's lymphoma Congenital malformations Spontaneous abortion or other adverse pregnancy outcomes
	2	Lindane and solvents	Breast cancer

TYPE OF CONCLUSION	GW&H Volume #	AGENT	HEALTH EFFECT
	1	Pyridostigmine bromide	Long-term adverse health effects
	1	Sarin at low doses insufficient to cause acute cholinergic signs	Symptoms and subsequent long-term adverse health effects
	Sarin Update	Sarin at low doses insufficient to cause acute cholinergic signs	Subsequent long-term cardiovascular effects Symptoms and subsequent long-term adverse neurological health effects
Inadequate/ Insufficient Evidence to Determine Whether an Association Exists (continued)	2	Solvents	Alterations in liver function tests after cessation of exposure Bone cancer Chronic pancreatitis and other persistent gastrointestinal outcomes Cirrhosis Long-term hearing loss Long-term reduction in color discrimination Long-term reduction in olfactory function Melanoma or nonmelanoma skin cancer Multiple sclerosis Oral, nasal, or laryngeal cancer Ovarian or uterine cancer Prostate cancer Stomach, rectal, or pancreatic cancer Systemic rheumatic diseases: scleroderma, rheumatoid arthritis, undifferentiated connective tissue disorders, and systemic lupus erythematosus
	2	Solvents other than tetrachloroethylene and dry-cleaning solvents	Esophageal cancer Bladder cancer Lung cancer
	2	Solvents other than trichloroethylene	Cervical cancer
	2	Solvents other than trichloroethylene and mixtures of benzene, toluene, and xylene	Colon cancer
	2	Solvents, parental preconception exposure	Congenital malformations Neuroblastoma and childhood brain cancers Spontaneous abortion or other adverse pregnancy outcomes
Inadequate/ Insufficient Evidence to Determine Whether an Association Exists (continued)	2	Solvents: specific, other than benzene	Acute and adult leukemia Aplastic anemia Brain and other central nervous system cancers Non-Hodgkin's lymphoma

TYPE OF CONCLUSION	GW&H Volume #	AGENT	HEALTH EFFECT
	1	Uranium	Bone cancer Cardiovascular effects Dermal effects Effects on hematological parameters Gastrointestinal disease Genotoxic effects Hepatic disease Immune-mediated disease Lymphatic cancer Musculoskeletal effects Nervous system disease Nonmalignant respiratory disease Ocular effects Reproductive or developmental dysfunction
	1	Uranium at higher levels of cumulative exposure (>200 mSv or 25 cGy)	Lung cancer
	1	Vaccination: anthrax	Long-term adverse health effects
	1	Vaccination: botulinum toxoid	Long-term adverse health effects
	1	Vaccinations: multiple	Long-term adverse health effects
Limited/Suggestive Evidence of No Association	1	Uranium at cumulative internal dose levels lower than 200 mSv or 25 cGy	Lung cancer
	1	Uranium	Clinically significant renal dysfunction
Consensus Not Reached on Category of Association	2	Tetrachloroethylene and dry-cleaning solvent	Esophageal cancer Lung cancer
	2	Trichloroethylene	Colon cancer Cervical cancer
	2	Mixtures of benzene, toluene, and xylene	Colon cancer
	2	Solvents	Kidney cancer
	2	Benzene and solvents	Brain and other central nervous system cancers
	2	Solvents, Parental preconception exposure	Childhood leukemia
	2	Organophosphorous insecticide exposure without OP poisoning	long-term neurobehavioral effects (that is, abnormal results on neurobehavioral test batteries and symptom findings)

APPENDIX B - Preface from:

Gulf War and Health Volume 3: Fuels, Combustion Products, and Propellants

PREFACE

As this report goes to press and our country is engaged in a war in Iraq, it is important to recall the 1990-1991 Gulf War. Engaging around 700,000 US military personnel, the Gulf War was of brief duration and entailed very few casualties among US troops. Yet, as they say, "war is hell", and our troops were exposed to numerous traumatic events and a multitude of hazardous substances. Not long after the war ended, many of its veterans reported a variety of chronic symptoms. Numerous studies were conducted, most of which corroborated reports of higher rates of signs and symptoms among these veterans. Some of the signs and symptoms have clearly been associated with identifiable medical diagnoses such as post-traumatic stress disorder and depression; others are outside current medical diagnostic classifications.

Veterans have been deeply concerned about whether exposures in the gulf were associated with chronic health problems after the end of the war. In response to their concerns, the Department of Veterans Affairs (VA) and Congress secured the assistance of the Institute of Medicine (IOM) in evaluating the scientific literature regarding exposures that may have occurred in the Gulf War. In a sense, this approach followed a model developed for the Vietnam War, after which there was concern about the possible health effects of exposure to dioxins in Agent Orange. In that case, the work of IOM has played a key role in informing VA decisions regarding compensation for dioxin-related chronic health effects. Following that model, Congress enacted legislation that specifically directed IOM to evaluate the effects of 33 agents; this report covers a small number of the agents: hydrazines, red fuming nitric acid, hydrogen sulfide, oil-fire byproducts, and diesel-heater fumes. In addition, VA requested that we assess potential exposures to fuels that were used in the Gulf War (gasoline, jet fuel, diesel fuel, and kerosene) and their combustion products.

Although we had a relatively small number of substances to review, the scientific literature on air pollutants from fuel combustion, as well as from exposure to fuels, is extensive. IOM appointed a committee with knowledge in the toxicology and epidemiology of fuels and combustion products; it included experts in combustion chemistry, rocket propellants, immunology, pulmonology, cancer, neurosciences, dermatology, and reproductive and developmental toxicology. The committee did not limit itself to studies of Gulf War veterans but rather reviewed all relevant literature with regard to chronic medical effects of exposure. Although the committee focused on epidemiologic studies, which are likely to identify associations between specific exposures and diagnoses in people, it also placed weight on toxicologic studies and on

clinical case series that were informative about specific exposure-disease relationships. Along the lines of earlier Gulf War reports, the committee has framed its conclusions in categories of strength of association. Despite the extensive challenge of reviewing the literature and the diversity of expertise and views among committee members, the committee was able to reach consensus on all conclusions. For that, I am most grateful.

The committee identified several associations between exposures to rocket propellants and combustion products and disease. However, there is some concern among our members about the direction that the process has taken. Many of the substances to which there was potential exposure in the gulf are unique to war service (for example, nerve agents, mustard agents, and rocket propellants), but others are not and may be at least as likely to occur in noncombat military service or in civilian life as in war (for example, fuels, air pollutants, and the solvents and pesticides reviewed in *Gulf War and Health, Volume 2: Insecticides and Solvents*). Therefore, as the process has evolved from an examination of exposures unique to wartime to exposures that are ubiquitous and may be even greater in civilian life, what are VA and Congress to do with the results of this study? A second troubling issue is the lack of exposure information for individual veterans; given that many risks are clearly exposure-related, it is difficult to use the results of our review to assess whether veterans' illnesses are due to such exposures. Third, it is important to interpret the results of our review in a larger context of public health and prevention; for example, the committee found some evidence of an association between hydrazine exposure and lung cancer, but there obviously are much larger and better-established associations between lung cancer and other exposures, such as smoking and exposure to radon and asbestos. Given those circumstances, this report cannot answer the question of whether service in the gulf was associated with such exposures and whether specific health outcomes are due to the exposures. Despite those limitations, the committee hopes that its report will be helpful to all who may have been exposed to the substances in question and to those who are considering further research in the subject.

I am deeply appreciative of the expert work of our committee members, and it has been a privilege and a pleasure to work with the IOM staff. Without them, this report would not have been possible.

Lynn Goldman, MD, MPH, *Chair*